PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
MJL/C1683.1/M		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/004215	04.10.2004	03.10.2003

International Patent Classification (IPC) or national classification and IPC
C07K14/705, A61K31/7076

Applicant
MEDICAL RESEARCH COUNCIL et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29.04.2005	30.08.2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/004215

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-21	as originally filed
Claims, Numbers	
1-21	as originally filed
Drawings, Sheets	
1/6-6/6	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-21 (all partially)

because:

☒ the said international application, or the said claims Nos. 1-8 and 20 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-21 (all partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☒ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/004215

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	8, 12, 13, 16 and 19-21
	No:	Claims	1-7, 9-11, 14, 15, 17 and 18
Inventive step (IS)	Yes:	Claims	8, 12, 13, 16 and 19-21
	No:	Claims	1-7, 9-11, 14, 15, 17 and 18
Industrial applicability (IA)	Yes:	Claims	9-19 and 21
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Citations

The documents mentioned in this Written Opinion are numbered as in the International Search Report (ISR), i.e. **D1** and **D6** correspond to the first and the last document of the search report, respectively. The ISR has been established by this authority.

Re ITEM III (Non-establishment of opinion)

1 No search report was established for the subject-matter of claims 1-21 (all partially). Consequently, preliminary examination has not been carried out for said claims (Rule 66.1(e) PCT). The International Preliminary Examining Authority (IPEA) agrees with the objection put forward by the International Searching Authority (ISA):

1.1 Claims 1-3 and 5-21 cover all substances/the use of all substances having the desired characteristic of modulating, stimulating or activating, respectively, the $P2X_7$ receptor. However, the application provides support (Art. 6 PCT) and disclosure (Art. 5 PCT) for only a limited number of such substances. Thus, a meaningful search over the whole of the scope claimed is impossible. Consequently, search and examination have been limited to the substances defined on p. 6, last par.-p. 7, l. 2 and their use (ATP, ATP analogues) (cf. Art. 17(2)(a)(ii) PCT).

1.2 Claim 4 covers all immunoglobulin or immunoglobulin-like variants which possess specific binding activity for the $P2X_7$ receptor and having the desired characteristic of modulating or stimulating, respectively, the $P2X_7$ receptor. However, the wording on p. 7, first full par., l. 1-3 shows that the application provides support (Art. 6 PCT) and disclosure (Art. 5 PCT) for no such immunoglobulin or immunoglobulin-like variants: "Other substances which the inventors predict might stimulate the $P2X_7$ receptor include antibodies and antibody-like variants with specific binding affinity for the $P2X_7$ receptor".

2 Claims 1-8 and 20 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT (*in vivo* treatment or diagnostic methods practiced on the human or animal body). Consequently, no opinion will be formulated with respect to the the industrial applicability of the subject-matter of

these claims (Art. 34(4)(a)(i) PCT).

Re ITEM V (Novelty, inventive step, industrial applicability)

1 **Novelty (Art. 33(2) PCT)**

1.1 The subject-matter of claims 8, 12, 13, 16 and 19-21 has not been made available to the public by any of the available prior art documents and can therefore be regarded as novel.

1.2 The subject-matter of claims 1-7, 9-11, 14, 15, 17 and 18 does not meet the requirements of Art. 33(2) and 33(3) PCT.

1.3 **D1** (Sanz et al.) discloses a method of increasing the effective intracellular concentration of tenidap, an anti-inflammatory drug, within a cell expressing a $P2X_7$ receptor comprising contacting the cell with said drug and ATP which stimulates the $P2X_7$ receptor (see e.g. abstract). The subject-matter of claims 1, 2, 4-7, 9-11, 14, 15, 17 and 18 can thus not be regarded as novel. **D1** further teaches that cytotoxic effects are visible after treatment of the cells with ATP and tenidap. The subject-matter of claim 3 can thus also not be regarded as novel.

1.4 Attention is drawn to the fact that the term "therapeutic molecule" is vague, practically any substance can be considered to fall under said term. **D2** (Verhoef et al.) discloses a method of increasing the effective intracellular concentration of YoPro dye within a cell expressing a $P2X_7$ receptor comprising contacting the cell with said dye and ATP/BzATP which stimulates the $P2X_7$ receptor (see e.g. p. 5732, left col., middle). The subject-matter of claims 1, 2, 4-7, 9-11, 14, 15, 17 and 18 can thus not be regarded as novel.

1.5 Similar results have been disclosed in **D3** (US6509163) (see e.g. Fig. 7) which therefore also deprives novelty of claims 1, 2, 4-7, 9-11, 14, 15, 17 and 18 (Art. 33(2) and (3) PCT).

2 **Inventive step (Art. 33(3) PCT)**

2.1 The subject-matter of claims 8, 12, 13, 16 and 19-21 cannot be derived from the available prior art in an obvious manner and therefore complies with the

requirements of Art. 33(3) PCT.

2.2 The combination of CD45 inhibition and P2X7 receptor modulation has not been disclosed or suggested in the available prior art (claims 8, 13, 16 and 19). The prior art does not disclose or suggest the inhibition of an efflux protein as defined in claims 12, 20 and 21.

3 **Industrial application (Art. 33(4) PCT)**

Claims 9-19 and 21 meet the criteria as set forth by Art. 33(4) PCT.

Re ITEM VII (Certain defects in the international application)

The present application contains such a high number of independent claims that the application as a whole lacks conciseness (Rule 6.1(a) PCT).